DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/23/2010 has been entered.

Status of Claims

Claims 1-11, 13, 14, 16 and 19-22 are cancelled. Claims 12, 15, 17 and 18 are currently pending and under consideration.

Withdrawn Rejections/Objections

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn in view of the amendments filed 3/23/2010. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

Claim 12 is objected to because of the following informalities:

Claim 12 provides "comprise" in line 16. It is suggested that applicant make the limitation plural; i.e. "comprises" to result in grammatical correctness. Likewise, it is suggested that "spot" be made plural "spots" in line 19. Further, it

is suggested that "form" be replaced with "from" in line 19 to result in grammatical correctness.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 15, 17 and 18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites "the proteome standard is one or more proteins selected from the group consisting of the spots in table 1; and diagnosing said subject with breast cancer when said proteome is indicative of said subject having breast cancer". The metes and bounds of the limitation are unclear because table 1 (specification, page 18) only recites number identifiers, molecular weights and isoelectric points. One skilled in the art would be uncertain what proteins correspond with the number identifiers, molecular weights and isoelectric points. Likewise, one skilled in the art would be uncertain how to diagnosis a patient as having breast cancer from a two-dimensional image "serum proteome pattern" when there is no information what proteins the "spots" of table 1 are and there does not seem to be a "proteome pattern" in Table 1 from which to compare.

Claim 12 recites the limitation "said step of producing" in line 16. There is insufficient antecedent basis for the limitation because no producing step was

previously recited. Examiner suggests replacing the limitation with "said step of generating".

Claim 12 recites the limitation of "optimal features playing a critical role in classification" in line 22. It is understood from the specification that "optimal features are "specific combinations of disease specific spots", page 8. However the metes and bounds of the limitation are unclear as it is unclear what combination would be deemed to be "optimal." It is unclear what the "features" are that play a "critical role" in classification. Likewise, it is unclear what is meant by a "critical role", i.e. what are the criteria by which one can judge whether a feature plays a "critical role"?

Claim 12 recites the limitation "estimating fidelity of the optimal feature data discriminated by the genetic algorithm by a support vector machine using estimation functions and classification error rates" in lines 23-25. It is unclear what the estimation of "fidelity" is with respect to "optimal feature data". It is unclear what the "classification error rates" are with regard to a determination of "fidelity". For purposes of applying the prior art, the "estimating fidelity of the optimal feature data discriminated by the genetic algorithm by a support vector machine using estimation functions and classification error rates" is interpreted to mean producing specific patterns or clusters of spots associated with a specific disease, wherein the patterns or clusters can deviate in position.

Claim 12 recites the limitation "the computed features" in the penultimate line of the fuzzy data mapping step. The term "the computed features" has no

antecedent basis. There are steps of extracting feature data from images, extracting feature data, extracting basic features, producing feature data, performing a genetic algorithm to discriminate optimal features, and extracting optimal feature data, but there is no step of COMPUTING features. It is unclear which, if any, of the many steps of extracting/producing features and feature data, is intended to provide the antecedent basis for "the computed features" recited in the third line of the fuzzy data mapping step.

Claim 12 recites the limitation "and thus creating a final rule base" in the last line. This limitation is unclear as the limitation "final rule base" is not recited anywhere else in the claim. The wherein step in which this term appears is a further limitation of a step of generating a proteome standard. The step of generating a proteome standard is followed by a step of constructing a database. It is noted that no actual step of generating a proteome standard is recited in the wherein clause. It is unclear whether the "final rule base" is intended to BE the proteome standard, or is intended to be the database of the construction step, is not intended to be a database at all (i.e. is intended to be a set of rules to be used in the construction step), or whether some other limitation is intended. For purposes of applying the prior art, the "final rule base" is interpreted to be guidelines of the classification step.

Response to Arguments

Applicant's arguments filed 3/23/2010 have been fully considered but they are not persuasive.

Applicants argue that claim 12 has been amended to recite that the proteins are identified by molecular weight and isoelectric point. Applicants submit that the proteins are made definite by their molecular weights and isoelectric points and their specificity to breast cancer, as described in the specification.

Applicant's arguments are not persuasive. Applicant still has not provided which proteins correspond with their respective identifier, molecular weight and isoelectric point. Neither has applicant provided how to diagnosis a patient as having breast cancer from a two-dimensional image "serum proteome pattern" when there is no information what proteins the "spots" of table 1 are and there does not seem to be a "proteome pattern" in Table 1 from which to compare.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyagi et al. (US 4,338,811) in view of Vachtesvanos et al. (US 6,650,779) and in view of Karlsen et al. (Opt. Eng., 2000, 39(3), 704-711) in view of Sidransky (Nature Reviews, 2002, 2, 210-219), as supported by Bray et al., (Cancer Research, 1987, 47, 5853-5860).

The instant claims provide a method of diagnosing breast cancer using a proteome image mining tool comprising creating a database of proteome standard from optimal features of 2D images from the serum proteome of normal individuals and individuals with breast cancer, extracting features from the 2D image of the serum proteome of a subject of interest, and comparing the subject's proteome pattern to the proteome standard pattern for breast cancer diagnosis, wherein the proteome standard is one or more proteins selected from

the spots of table 1, wherein said proteome standard comprises molecular weights and isoelectric points of said proteins; and diagnosing said subject with breast cancer when said proteome is indicative of said subject having breast cancer. The step of generating the proteome standard is limited to comprise: a step of pre-processing, including an image processing step of performing noise filtering, image enhancement, ortho-projection and edge detection from the two-dimensional proteome images, a feature extraction step of extracting basic features (disease-specific spots) from the image-processed two-dimensional images and producing feature data by labeling each of the extracted basic features. The step of generating the proteome standard is also limited to comprise an evolutionary classification step of performing a genetic algorithm to discriminate optimal features (producing patterns of individuals having a specific disease) by producing specific patterns or clusters of spots associated with a specific disease, wherein the patterns or clusters can deviate in position. The mapping step is limited to comprise classifying the optimal features with a statistical method and quantifying the classification using a fuzzy technique. The step of rule-based classification is limited to using guidelines for the classification step.

In light of the indefiniteness of the identification of spots and lack of proteome standard pattern in table 1, the limitation "wherein the proteome standard is one or more proteins selected from the spots of table 1, wherein said proteome standard comprises molecular weights and isoelectric points of said

proteins" will be interpreted to comprise any known breast cancer marker which has a molecular weight and isoelectric point as set forth in Table 1.

Regarding claims 12 and 18, Miyagi et al. shows a disease diagnostic method in which a 2D pattern diagram representing substances in a body fluid of a subject, is compared for disease diagnostic purposes with a 2D pattern diagram that met particular thresholds (optimal features), stored in a file, representing substances from normal and abnormal patients classified by diseases, (abstract; column 2, line 52 – column 3, line 49).

Miyagi et al. does not show the image pre-processing step and classification step with a genetic algorithm or the fidelity estimation using a SVM or show fuzzy data mapping, quantifying statistical inaccuracy using a fuzzy technique and a rule-based classification step, or serum features associated with breast cancer.

Vachtesvanos et al. shows pre-processing a digitized 2D image including edge detection enhancement, de-noising, projection onto an orthonormal basis function, (column 8, lines 10-43; column 24, lines 3-50) and labeling extracted features, (column 10, lines 1-18). Vachtesvanos et al. shows a genetic algorithm employed to train a wavelet neural network for classification, (column 22, lines 1-10). Vachtesvanos et al. shows estimation functions and classification error rates, (column 21, lines 18 – column 22, line 10). Vachtesvanos et al. shows mapping from a feature space to a decision space, where detection and classification can occur by fuzzy logic, e.g. fuzzy C-Means, fuzzy relational matrix, fuzzy rule-base classification, etc., (column 3, line 35 - column 4, line 23).

Vachtesvanos et al. shows that fuzzy C-means can assign a degree of association of a feature with a partition, (quantifying a statistical inaccuracy of a classification), (column 4, lines 50-65).

Miyagi et al. and Vachtesvanos et al. do not show a SVM or serum features associated with breast cancer.

Karleen et al. shows a SVM algorithm classifier of features from images compared to classification by a plurality of neural networks, using estimation functions and classification error rates, (abstract, page 704, right column, second paragraph; page 706, left column; page 708; page 709, right column; Figure 6).

Miyagi et al., Vachtesvanos et al. and Karleen et al. do not show serum features associated with breast cancer.

Sidransky shows proteins that are known markers from patient serum associated with breast cancer, ERBB2 (HER2/neu), CA15-3 (MS1), CEAsd, CA125, (page 210, right column; page 215, right column; Table 1; Figure 2).

Bray et al., shows molecular weights and isoelectric point of common serum markers associated with breast cancer, CA-549, (abstract; page 5858, right column, second paragraph), thereby supporting that the cancer markers of Sidransky have molecular weights and isoelectric points as disclosed in instant Table 1.

Regarding claim 18, Miyagi et al. shows a database of pattern diagram data of the subject and analysis results recorded, (Figure 4).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of disease diagnosis of Miyagi et al.

with the image pre-processing and feature classification by Vachtesvanos et al., the classification SVM algorithm by Karlsen et al. and the serum proteomic data related to breast cancer by Sidransky because Vachtesvanos et al. shows that image pre-processing enhances the real signal and improves the quality of feature extraction while the multidimensional neural network analyzes and identifies patterns efficiently and economically while lessening the need for human assistance (column 12, lines 57-61; abstract), Karlsen et al. shows that the SVM algorithm gives higher correct classification results compared to neural networks, (abstract), and a proteome pattern comparison is a useful diagnostic tool for identifying cancer in a patient (Sidransky, Figure 2). There would have been a reasonable expectation of success for combining Vachtesvanos et al., Karlsen et al. and Sidransky with Miyagi et al. because all are methods that identify features and classify patterns.

Claims 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyagi et al. (US 4,338,811) in view of Vachtesvanos et al. (US 6,650,779) in view of Karlsen et al. (Opt. Eng., 2000, 39(3), 704-711) in view of Sidransky (Nature Reviews, 2002, 2, 210-219), as supported by Bray et al., (Cancer Research, 1987, 47, 5853-5860), as applied to claims 12 and 18 above, and further in view of Srinivas et al. (Clinical Chemistry, 2001, 47(10), 1901-1911).

The instant claims 15 and 17 depend from claim 12 with the extra limitations that for step 1) extracting correlations between spots utilizes

experimental knowledge and a statistical method, and classifying the extracted correlations utilizes a statistical method (claim 15); and for step 3) pattern matching of the subject utilizes features, estimation functions and a fine classification step (claims 17).

Miyagi et al., Vachtesvanos et al., Karlsen et al. and Sidransky are applied to claims 12 and 18 above.

Regarding claims 15 and 17, Miyagi et al. shows peak areas of substances are integrated with respect to a preset slope reference, (Figure 2A) and retention times of peaks is subject to variation (experimental variation), where the 2D pattern diagram shows the relation between peak retention times and levels to be used for the disease diagnosis, (column 3, line 1 – column 4, line 14). Miyagi et al. shows that in the course of creating a pattern diagram, a correlation coefficient taking into account the importance of each individual peak or substance in relation to the diagnosis may be used to modify the peak level or area, in the process of disease diagnosis by comparison of the pattern diagrams (column 3, second paragraph; column 4, lines 57-62). Miyagi et al. teaches a subject's chromatogram compared to a reference chromatogram with a chemical control, and peak matching for eliminating deviation, i.e. eliminating systematic and analysis errors, (column 6, oines 22-34).

Miyagi et al., Vachtesvanos et al., Karlsen et al. and Sidransky do not show correlating and classifying by a statistical method; nor a fine classification step.

Srivinas et al. shows software packages and bioinformatics tools to analyze two-dimensional gel electrophoresis (2DE) protein patterns, including tools that help in segmentation and detection of protein spots on the images, matching and edition; additional features include pattern recognitions capabilities and the ability to perform multivariate statistics, (page 1907, left column, second paragraph; Figure 4). Srivinas et al. shows protein data derived from 2DE analysis has been used to develop artificial learning models to help classify tumors into benign, borderline, and malignant; and statistical algorithms such as partial least squares and hierarchical clustering have been used to that effect, (page 1907, right column, second to last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of disease diagnosis of Miyagi et al., Vachtesvanos et al., Karlsen et al. and Sidransky with the statistical clustering and pattern matching by Srinivas et al. because by Sidransky shows that bioinformatic tools are needed at all levels of proteomic analysis (page 1906, right column, last paragraph) and Srinivas et al. shows that automated techniques in clustering and pattern matching substantially reduce the amount of knowledge required by users and proteomics is essential in determining those changes in protein profiles that can lead to a more comprehensive understanding of the disease process, (page 1907, right column, first paragraph; page 1908, right column, first paragraph).

Response to Arguments

Applicant's arguments filed 3/23/2010 have been fully considered but they are not persuasive.

Applicants argue that the cited art does not teach the limitations of the amended claims. Applicants argue that none of the markers cited in the prior art are markers shown by molecular weight and isoelectric point as those in Table 1. Applicants argue that there is not motivation to combine the above cited art with a reasonable expectation of success.

Applicants arguments are not persuasive.

Applicants still have not provided what proteins correlate to identifiers, molecular weights and isoelectric points, See above. Thus the claims are interpreted as reciting any known breast cancer marker which has a molecular weight and isoelectric point as set forth in Table 1. Bray et al. meets this limitation. See above. There is motivation and reasonable expectation of success to combine the cited art, see above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY D. RIGGS II whose telephone number is (571)270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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